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Cardiovascular prognostic factors, gamma glutamil transferase levels and other biochemical parameters related to morbidity and mortality in COVID-19

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ABSTRACT

Aims: COVID-19 may exacerbate cardiovascular risk factors and pre-existing cardiovascular disease or lead to the development of new cardiovascular complications. Gama glutamil transferaz (GGT) is an enzyme found in the cell membranes of many tissues, especially the liver, bile duct and kidneys. Recent studies have shown that increased GGT levels are strongly associated with prognosis in cardiopulmonary disorders. Studies to date have reported on the increased predictive value of serum GGT level for cardiovascular disease and have shown marginal improvements in risk estimation. In the light of all this information, in this study, it was aimed to investigate the effect of serum GGT level on the clinical classification of the disease, cardiovascular risk and morbidity and mortality in COVID-19, in addition to known cardiovascular prognostic markers.

Methods: The study included 128 patients over the age of 18 who were found to have positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in the nasopharyngeal and oropharyngeal samples taken during their admission to Kahramanmaraş Sütçü İmam University (KSU) Medical Faculty Chest Diseases Outpatient Clinic And Emergency Department. According to the most recently published 2019 novel coronavirus pneumonia diagnosis and treatment program (version 7), COVID-19 disease is divided into groups as mild, moderate, severe and critical illness. Demographic data, comorbidities, symptoms and signs, laboratory findings, and chest computed tomography (CT) scans were reviewed. The presence of heart failure, coronary artery disease or arrhythmia in the included patients was defined as cardiovascular disease. Patients were excluded if they were younger than 18 years old, pregnant, had a history of hepatobiliary disorders, alcohol abuse or other acute illnesses, died at the time of admission, had incomplete baseline data, or were transferred to other designated hospitals during hospitalization.

Results: Fifty-five (43%) of the participants were female and 73 (57%) were male, with a mean age of 55.6 years. When examined in terms of age, the difference between the groups was statistically significant. The difference between the individuals with and without hypertension and diabetes mellitus was found to be significant in terms of disease severity. When examined in terms of symptoms, 23 (71.9%) of the patients in the mild group were symptomatic, 9 (28.1%) were asymptomatic, and all of the patients in the moderate, severe and critical groups were symptomatic (100%). Cardiovascular biomarkers and GGT values were found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. However, having cardiovascular disease did not cause a significant difference in GGT levels fo the disease groups. GGT levels were found to be statistically similar in individuals with and without the disease. When blood gas parameters were analyzed in terms of disease severity, oxygen saturation (SpO_2) and PO_2 were found to be significantly lower in the severe and critical illness group than in the mild and moderate disease group. When the effect of blood parameters on mortality was analyzed by logistic regression analysis, only the effect of PO_2 parameter on mortality was found to be statistically significant. In addition, the effects of cardiovascular diseases and age variables on mortality were found to be statistically significant (p=0.031, p=0.007; respectively). The effect of cardiovascular disease on mortality was 4,325 times (ODDS ratio) higher compared to individuals without cardiovascular diseas.

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Conclusion: In this study, we determined two important findings. First, the serum level of GGT was found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. Second, cardiovascular disease, advanced age, and hypoxemia were associated with mortality from COVID-19 disease. Although GGT provides no increased benefit for predicting cardiovascular disease risk, its potential causal relationship with cardiovascular disease deserves attention.

Keywords: COVID-19, gama glutamil transferaz, GGT, cardiovascular disease, mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China in late December 2019. Since then, COVID-19 has spread rapidly around the world, becoming a global pandemic affecting more than 200 countries and regions.[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, non-segmented, single-stranded, positive RNA virus belonging to the coronaviridae family.[2] This novel coronavirus enters cells through binding of the viral surface spike protein to the angiotensin converting enzyme (ACE) 2 protein. ACE2 is highly expressed in lung alveolar cells and provides the virus entry route.[3] ACE2 is also commonly found in the myocardium, which raises concerns due to the possibility of direct viral infection of the cardiovascular system.[4]

Although COVID-19 patients primarily present with respiratory symptoms and therefore follow a pneumonia-like treatment plan, it is important not to ignore the cardiovascular system when following these cases and to recognize those presenting with early signs of acute myocardial injury. COVID-19 may exacerbate cardiovascular risk factors and pre-existing cardiovascular disease or increase susceptibility to the development of new cardiovascular complications.[5]

During the COVID-19 outbreak, it is necessary to evaluate patients at increased risk of adverse cardiovascular disease outcomes and/or myocardial injury with biomarkers such as serum cardiac troponin I (cTnI), brain natriuretic peptide (BNP), and creatine kinase-myocardial band (CK-MB). While these biomarkers are recognized for cardiovascular disease, they may aid the prognosis of COVID-19, particularly in those with cardiovascular comorbidities or risk factors that predispose to disease worsening.[6,7]

Identifying any new biomarkers early in the course of COVID-19 that indicate significant morbidity or mortality is also important as it can help prevent this rapid worsening later on. It is well known that GGT is increased in hepatobiliary dysfunction and alcohol abuse. Recent studies have shown that increased GGT levels are strongly associated with prognosis in cardiopulmonary disorders such as heart failure, acute myocardial infarction, and coronary artery disease.[8]

Studies to date have reported on the increased predictive value of serum GGT level for cardiovascular disease and have shown marginal improvements in risk estimation. In the light of all this information, in this study, it was aimed to investigate the effect of serum GGT level on the clinical classification of the disease, cardiovascular risk and morbidity and mortality in COVID-19, in addition to known cardiovascular prognostic markers.

METHODS

Study Population and Study Design

Our study was planned as a single-center, retrospective observational cohort study, and patients between March 2020 and December 2020 were screened from the hospital electronic data system. The study protocol was approved by the Turkish Ministry of Health General Directorate of Health Services Scientific Study Platform and Kahramanmaraş Sütçü İmam University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 14.09.2021, Decision No:07). The study was conducted in line with the ethical principles of the Declaration of Helsinki revised in 2013.

The study included 132 patients over the age of 18 who applied to the KSU Faculty of Medicine Chest Diseases outpatient clinic and emergency department and were hospitalized with positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) in their nasopharyngeal and oropharyngeal samples taken during their admission. Patients who were clinically diagnosed with COVID-19 without PCR confirmation were excluded from the study. According to the most recently published 2019 novel coronavirus pneumonia diagnosis and treatment program (version 7) COVID-19 patients are divided into mild, moderate, severe and critical classes.[17] Accordingly, the definitions of the disease are as follows:

Mild disease: Defines mild clinical symptoms and no signs of pneumonia on imaging.

Moderate disease: Defines the radiological findings of pneumonia with fever and respiratory symptoms.

Severe disease: Meeting any of the following criteria: Respiratory distress (≥30 breaths/min); Oxygen saturation at rest <93%; Partial arterial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <300 mmHg (1 mmHg=0.133 kPa). Defines the condition in which the infiltration has spread to more than 50% of the lungs on chest imaging within 24-48 hours.

Critical disease: Meeting any of the following criteria: Defines respiratory failure and requiring mechanical ventilation, septic shock and/or multiple organ failure.

Patients <18 yo, pregnant women, those with a history of hepatobiliary disorder, alcohol abuse, or other acute illness, patients who died at admission, had missing baseline data, or were transferred to other designated hospitals during hospitalization were excluded from the study. Therefore, 128 patients were included in the final analysis. Informed consent was waived since the data used in the study were anonymous. Patients' demographic data, comorbidities, symptoms and signs, laboratory findings, and chest computed tomography (CT) scans were reviewed. The presence of heart failure, coronary artery disease or arrhythmia in the included patients

was defined as cardiovascular disease. All data were obtained from the electronic hospital information system. Peripheral venous blood samples were evaluated in the central laboratory of the university hospital following standard procedures.

Routine blood tests (including leukocyte count and leukocyte subtypes, hemoglobin count and platelet count) were measured with a Sysmex XN-1000 automated hematology analyzer (Sysmex XN-1000 Corporation, Kobe, Japan). Cobas 8000 biochemistry analyzer (Cobas 8000 c702 biochemistry analyzer Roche Diagnostics Gmbh, Mannheim, Germany) was used to measure biochemical parameters. Blood coagulation tests including plasma D-dimer, prothrombin time (PT), international normalized ratio (INR), activated partial prothrombin time (APTT), and thrombin time (TT) were measured using a Sysmex CS-2500 coagulation analyzer system (Sysmex XN-1000 Corporation, Kobe, Japan). RNA isolation was performed with the Bi-Speedy viral nucleic acid isolation kit (Bioeksen, Istanbul, Turkey) according to the manufacturer's instructions. PCR was performed with the Bio-Speedy COVID-19 RT-qPCR detection kit (Bioeksen, Istanbul, Turkey) on the Rotor-Gene Q device (Qiagen, Hilden, Germany).

Statistical Analysis

In the evaluation of the data, the conformity of the variables to the normal distribution was examined with the Kolmogorov Smirnov test. Group comparisons in normally distributed variables were performed with Independent Samples T-test and one-way analysis of variance. In the variables not normally distributed, Mann Whitney U test and Kruskal Wallis H test were used. Frequency distribution between categorical variables was examined using Chi-square test and Fisher's Exact Chi-square test. The effects of independent variables on dependent variables were analyzed by logistic regression analysis. Statistical parameters were expressed as median (Quartile 25% –Quartile 75%), mean±SD, and n (%). Statistical significance was accepted as $p<0.05$. IBM SPSS version 22 software and R.3.3.2 software were used to evaluate the data.

RESULTS

A total of 128 patients who met the inclusion criteria were included in the study. Fifty-five (43%) of the participants were female and 73 (57%) were male, with a mean age of 55.6. When examined in terms of age, the difference between the groups was statistically significant. The difference between the individuals with and without hypertension and diabetes mellitus was found to be significant in terms of disease severity. The demographic data of the patients are shown in **Table 1**.

When examined in terms of symptoms, 23 (71.9%) of the patients in the mild group were symptomatic, 9 (28.1%) were asymptomatic, and all of the patients in the moderate, severe and critical groups were symptomatic (100%). In the mild group, 7 patients (21.9%) had fever, 11 patients (34.4%) had cough symptoms, and no patient had respiratory distress. In the moderate group, fever was detected in 17 patients (53.1%), cough in 26 patients (81.3%), and respiratory distress in 23 patients (71.9%). In the severe group, fever was detected in 11 patients (34.4%), cough in 29 patients (90.6%), and respiratory distress in 29 patients (90.6%). In the critical group, fever was detected in 23 patients (71.9%), cough in 31 patients (96.9%), and respiratory distress in 31 patients (96.9%). Chi-Square test; a:0.05; * The distributional difference was found to be statistically significant (**Table 1**).

When analyzed in terms of biochemical parameters, the mean value of ALT was not significantly different between each group. However, other biochemical parameters were statistically significant between the groups (**Table 2**). Cardiovascular biomarkers and GGT values were found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. However, having cardiovascular disease did not cause a significant difference in GGT levels in the disease groups. GGT levels were found to be statistically similar in individuals with and without the disease.

When the median values of blood gas parameters were examined according to disease severity, oxygen saturation (SpO_2) and PO_2 were found to be significantly lower in the severe and critical disease group than in the mild and moderate disease group.

When the effect of blood parameters on mortality was analyzed by logistic regression analysis, only the effect of PO_2 parameter on mortality was found to be statistically significant (p 0,04) (**Tablo 3**). In addition, the effects of cardiovascular diseases and age variables on mortality were found to be statistically significant (p=0.031, p=0.007; respectively). The effect of cardiovascular disease on mortality was 4,325 times (ODDS ratio) higher compared to individuals without cardiovascular disease (**Tablo 4**).

DISCUSSION

In this study, we determined two important findings. First, the serum level of GGT was found to be significantly higher in the severe and critical disease group than in the mild and moderate disease group. Second, cardiovascular disease, advanced age, and hypoxemia were associated with mortality from COVID-19 disease.

Respiratory viral infections are generally associated with cytokine production, inflammation, cell death, and other pathophysiological processes that may be associated with redox imbalance or oxidative stress (OS). It is known that overproduction of reactive oxygen species (ROS) and lack of antioxidant mechanisms are crucial for viral replication and virus-associated disease.[10] Significantly elevated blood cytokine and chemokine levels have also been observed in patients with COVID-19 infection. "Cytokine storm" triggers a proinflammatory environment that is strongly associated with severe tissue damage and contributes to the fatal outcome of COVID-19 patients.[11] Many studies have shown that overproduction of ROS and a deprived antioxidant system play an important role in the pathogenesis of SARS-CoV infection, as well as in the progression and severity of respiratory disease. Increased ROS levels and impaired antioxidant defense have been demonstrated in experimental animal models of severe acute respiratory distress syndrome.[12]

GGT hydrolyzes the gamma-glutamyl bond between glutamic acid and cysteine, which is the first step in the extracellular hydrolysis of glutathione (GSH), which acts as an important antioxidant in cells, and provides the formation of cysteine, which is necessary for the re-synthesis of GSH in the cell.[13] It has been suggested that the pathway associated with GSH catabolism of GGT may also lead to the production of

Table 1. Demographic and clinical features of the groups

		Mild (n:32)	Moderate (n:32)	Severe (n:32)	Critical (n:32)	p
Age		41.3 (±15.4[c,d])	51.1 (±20.5[c,d])	63.8 (±13.5[a,b])	66 (±16.3[a,b])	p<0.001*
Gender	Female	18 (±56.3)	14 (±43.8)	12 (±37.5)	12 (±37.5)	0.545
	Male	2 (6.3%)	18 (±56.3)	20 (±62.5)	20 (±62.5)	
Cardiovascular disease (CVD)				7 (21.9%)	10 (31.3%)	0.095
Traditional risk factors for CVD			4 (12.5%)			
Hypertension (n,%)			4 (12.5%)	17 (53.1%)	15 (46.9%)	0.004*
Diabetes mellitus (n,%)			4 (12.5%)	10 (31.3%)	12 (37.5%)	0.031*
Smoking (n,%)		5 (15.6%)	2 (6.3%)	4 (12.5%)	6 (18.8%)	0.498
Body-mass index (kg/m^2)		26.25 (±3.18)	26.44 (±2.71)	25.89 (±2.77)	27.07 (±3.26)	
Signs and symptoms						
Fever		7 (21.9%)	17 (53.1%)	11 (34.4%)	23 (71.9%)	p<0.001*
Cough		11 (34.4%)	26 (81.3%)	29 (90.6%)	31 (96.9%)	p<0.001*
Muscle pain		13 (40.6%)	20 (62.5%)	12 (37.5%)	28 (87.5%)	p<0.001*
Sputum		2 (6.3%)	20 (62.5%)	27 (84.4%)	31 (96.9%)	p<0.001*
Sore throat		7 (21.9%)	9 (28.1%)	3 (9.4%)	4 (12.5%)	0.185
Diarrhea		4 (12.5%)	2 (6.5%)	0 (0%)	0 (0%)	0.053
Nausea		2 (6.3%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	0.726
Dizziness		0 (0%)	1 (3.1%)	0 (0%)	0 (0%)	0.388
Headache		10 (31.3%)	5 (15.6%)	4 (12.5%)	3 (9.4%)	0.095
Dyspnea		0 (0%)	23 (71.9%)	29 (90.6%)	31 (96.9%)	p<0.001*
Imaging features						
Consolidation		3 (9.4%)	4 (12.5%)	4 (12.5%)	0 (0%)	p<0.001*
Ground-glass opacity		2 (6.3%)	11 (34.4%)	13 (40.6%)	4 (12.5%)	p<0.001*
Consolidation + ground-glass opacity		5 (15.6%)	11 (34.4%)	15 (46.9%)	28 (87.5%)	p<0.001*
Clinical course						
Outpatient		6 (18.8%)	0 (0%)	0 (0%)	0 (0%)	p<0.001*
Ward inpatient		31 (96.9%)	31 (96.9%)	14 (43.8%)	2 (6.3%)	p<0.001*
Admission to ICU		0 (0%)	1 (3.1%)	18 (56.3%)	30 (93.8%)	p<0.001*
The need for noninvasive mechanical ventilation		0 (0%)	0 (0%)	11 (34.4%)	25 (78.1%)	p<0.001*
Intubation		0 (0%)	0 (0%)	2 (6.3%)	15 (46.9%)	p<0.001*
Discharged		32 (100%)	32 (100%)	2 (6.3%)	17 (53.1%)	p<0.001*
Died		1 (3.1%)	0 (0%)	2 (6.3%)	15 (46.9%)	p<0.001*

One way anova: Post-hoc: Tukey HSD test; Chi-Square: a:0.05; * The difference between groups is statistically significant; a The difference is significant with the mild group; b The difference is significant with the moderate group; c The difference is significant with the Severe Group; d The difference is significant with the critical group

Table 2. Laboratory findings of the study groups

	Mild (n:32)	Moderate (n:32)	Severe (n:32)	Critical (n:32)	p
Hematologic biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
WBC count	**6230** (4940-8320)	**5420** (4425-8620)	**7765** (6040-14855)	**7765** (6040-14855)	0.021
Neutrophil count	**3660** (2675-5395)	**3600** (2665-7085)	**6390** (4630-13140)	**5980** (4155-9065)	**p<0.001**
Lymphocyte count	**1775** (1285-2120)	**1260** (785-1535)	**865** (600-1065)	**705** (525-1180)	**p<0.001**
Platelet count	**228500** (196000-280000)	**196000** (147000-232000)	**229500** (198500-291000)	**185500** (154000-229500)	
Hemoglobin	**14.4** (13.4-15.8)	**13.1** (12.0-14.3)	**13.6** (11.7-14.2)	**12.7** (11.4-13.5)	**0.001**
Biochemical biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
GGT	**22.5** (15-36.5)	**25.5** (17-60.5)	**75** (26.5-121)	**42.5** (25-65.5)	**p<0.001**
ALT	**22** (15-36)	**20.5** (11.5-41.5)	**27.5** (18-42)	**27.5** (17.5-48.5)	0.202
AST	**23.5** (18.5-29)	**25** (19.5-32.5)	**36.5** (27.5-56.5)	**45** (26.5-81)	**p<0.001**
LDH	**209.5** (186.5-265.5)	**286.5** (205.5-353.5)	**470.5** (375-803)	**495.5** (336.5-709)	**p<0.001**
CK-MB	**2** (2-2.7)	**2** (1.9-2)	**2** (2-3)	**2.15** (2-3.84)	**p<0.001**
Troponin	**0.01** (0.01-0.01)	**0.01** (0.01-0.01)	**0.01** (0.01-0.01)	**0.01** (0.01-0.05)	**0.016**
Albumin	**46** (42.2-48)	**38.9** (34.9-42.8)	**34.3** (32.2-37.5)	**33.9** (30.5-36.3)	**p<0.001**
Coagulation biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
PT	**11.5** (11-12)	**12.1** (11.5-13)	**12.8** (12.1-14.1)	**13.2** (11.9-14.1)	**p<0.001**
D-dimer	**0.32** (0.19-0.45)	**0.34** (0.23 -1.00)	**1.03** (0.61-1.63)	**1.17** (0.90-2.4)	**p<0.001**
Inflammatory biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
CRP	**3.14** (3.14-6.26)	**25.40** (12.25-78)	**97.10** (52.55-169.5)	**106** (58.5-157)	**p<0.001**
Procalcitonin	**0.04** (0.03-0.06)	**0.08** (0.06-0.25)	**0.22** (0.11-0.58)	**0.22** (0.11-1.52)	**p<0.001**
Ferritin	**96.0** (42.5-175.5)	**187** (88.5-511)	**568.5** (440.5-793.5)	**547.5** (362-1172)	**p<0.001**
Arterial blood gas biomarkers	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	**Median** (Q1-Q3)	
Ph	**7.39** (7.37-7.40)	**7.40** (7.39-7.41)	**7.44** (7.40-7.47)	**7.42** (7.40-7.47)	**p<0.001**
PO_2	**82** (78-86)	**80** (75.5-84.5)	**47.3** (33-62.5)	**50.5** (35-62)	**p<0.001**
PCO_2	**40.2** (39-42)	**40.1** (39.7-42)	**38.5** (35-42)	**35.4** (31.8-43.4)	**0.020***
SO_2	**96** (95-97)	**95** (95-96)	**86** (77.2-92.8)	**87.45** (81.2-91.35)	**p<0.001**
HCO_3	**23.7** (23.4-24.1)	**23.9** (23.6-24.5)	**25.3** (23.5-27.9)	**25.2** (22.3-27)	0.060

GGT: Gama glutamil transferaz, CK-MB: Creatine kinase-myocardial band, PT: Prothrombin time

Table 3. Laboratory findings of the study groups

Arterial blood gas biomarkers	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	
Ph	**7.39** (7.37-7.40)	**7.40** (7.39-7.41)	**7.44** (7.40-7.47)	**7.42** (7.40-7.47)	**p<0.001**
PO_2	**82** (78-86)	**80** (75.5-84.5)	**47.3** (33-62.5)	**50.5** (35-62)	**p<0.001**
PCO_2	**40.2** (39-42)	**40.1** (39.7-42)	**38.5** (35-42)	**35.4** (31.8-43.4)	**0.020***
SO_2	**96** (95-97)	**95** (95-96)	**86** (77.2-92.8)	**87.45** (81.2-91.35)	**p<0.001**
HCO_3	**23.7** (23.4-24.1)	**23.9** (23.6-24.5)	**25.3** (23.5-27.9)	**25.2** (22.3-27)	0.060

Table 4. The effects of demographic characteristics and comorbid diseases of individuals on mortality

	Wald	p	ODDS ratio	ODDS ratio 95% confidence interval	
				Lower limit	Upper limit
Smoking	.955	.328	2.467	0.403	15.080
CVD	4.649	**.031***	4.325	1.143	16.374
DM	1.629	.202	2.467	.616	9.871
HT	.670	.413	0.547	0.129	2.320
Age	7.348	**.007***	1.070	1.019	1.124
Gender	.323	.570	0.680	0.180	2.569

Dependent variable: Patient discharge/ex status, Binary logistic regression: a:0.05, *The effect is statistically significant, CVD: Cardiovascular disease

prooxidant substances. It is thought that the more reactive thiol cysteinyl glycine, which is formed as a result of the effect of GGT in GSH metabolism, can reduce ferric ions to Fe(III) and ferrous ions Fe(II), and as a result, it can initiate iron redox cycle events that result in the production of ROS.[14] Low glutathione levels increase cellular oxidative stress and are associated with various disease states and immune dysfunctions leading to higher susceptibility to viral infections, i.e. uncontrolled SARS-CoV-2 infection.[15]

Uncontrolled replication causes oxidative damage to the lungs, which increases viral load, thereby increasing the severity of viral infection. Conversely, high GSH levels can prevent the virus from replicating efficiently, resulting in lower viral loads and therefore milder symptoms. In a study investigating the impact of GSH levels on the course of COVID-19 infection, high ROS/GSH ratios were found to be strongly associated with worsening symptoms and slower healing times.[16]

Severity of SARS-CoV-2 infection or COVID-19 disease and risk of death are associated with age.[17] In many previous studies, it has been reported that the disease course is more severe and leads to mortality in older patients with COVID-19 compared to young and middle aged ones.[18] The results of our study also confirmed that the severity of the disease increases significantly with increasing age, which was an independent risk factor for mortality.

A strong association has been reported between hypoxemia occurring during the course of COVID-19 and worsening clinical outcomes of the disease. In a study of 140 patients with COVID-19-related pneumonia, it was found that oxygen saturation (SpO_2) >90.5% predicted survival with 84.6% sensitivity and 97.2% specificity. Also, in this study, SpO_2 of 90% or less provided a more robust risk factor for mortality despite supplementation with oxygen. The severity of hypoxemia in COVID-19 patients is independently associated with in-hospital mortality and may be an important indicator of the patient's risk of admission to the ICU.[19] Also in our study, decreased SpO_2 and PO_2 values as the severity of the disease increased and PO_2 being a determinant factor of mortality, is a finding of significant prognostic value of hypoxemia for hospitalized patients with pneumonia associated with COVID-19, suggesting that it provides justification for applying standard scoring strategies to predict risk and guide treatment even in this patient population.[20,21] COVID-19 appears to be associated with a wide range of cardiovascular sequelae, including acute onset heart failure, arrhythmias, acute coronary syndrome, myocarditis, and cardiac arrest. In addition, acute cardiac injury appears to be significantly associated with increased in-hospital mortality in COVID-19 patients.[22]

Serum cTnI is the worldwide gold standard necrotic biomarker for myocardial risk assessment. Other biomarkers of myocardial injury with diagnostic value include creatine CK-MB and BNP, which may provide information about the severity of symptoms in COVID-19. Although they have already been established for cardiovascular disease, the potential role of these biomarkers, particularly cTnI, as prognostic predictors in COVID-19 patients has been demonstrated in several studies. In a meta-analysis of 4 studies including 341 COVID-19 patients, a significantly higher difference in mean cTnI was reported in patients with more severe COVID-19 symptoms than those with milder symptoms.[23] Similarly, in our study, as the severity of the disease in COVID-19 cases increased, the increase in cTnI level and its effect on the severity of the disease were statistically significant, and our study confirmed the potential value of cTnI in predicting the outcome of COVID-19 patients.

Therefore, a correlation between elevated serum cTnI levels and a higher risk of mortality in COVID-19 patients can be logically predicted.[24,25]

While cTnI has shown remarkable potential in predicting COVID-19 outcomes, BNP has also shown some hope in the prognosis of COVID-19. Guo et al.[26] found that elevated cTnT levels were significantly associated with elevated serum BNP levels. The authors reported that in addition to the gradual increase in serum cTnT levels, BNP levels gradually increased in patients with deteriorating health, while patients who were successfully discharged had low and stable serum BNP levels. Similar to previous studies, we think that in our study the fact that BNP levels were found to be significantly higher in severe and critical disease groups in our study reflects the possibility of routinely measuring serum BNP levels in COVID-19 patients to reduce negative negative outcomes during the course of COVID-19.

In addition to cTnI and BNP, CK-MB may have similar prognostic value in COVID-19. In a study by Wang et al.[27] 36 (26.1%) of 138 COVID-19 patients were admitted to the ICU with severe symptoms, and in all of these patients, serum cTnI and CK-MB levels were significantly elevated compared with patients who were not admitted to the ICU.-

. Therefore, we think that further studies that clearly demonstrate a clear link between CK-MB and BNP and COVID-19 outcomes will provide a better understanding of their prognostic role.

It is known that GGT activity is closely associated with cardiometabolic risk. With several reports showing an independent association of higher GGT levels with increased risk of cardiovascular disease, there is a growing debate that adding GGT measures to existing risk estimation algorithms may be associated with improvements in the ability to predict cardiovascular disease.[28] Various mechanisms have been proposed to explain the possible link between GGT and cardiovascular disease. These mechanisms include the associations between GGT and both classic and novel cardiovascular risk factors, oxidative stress and direct involvement of GGT in atheromatous plaque formation.[29] GGT is an enzyme primarily found in the liver and is often considered a marker of hepatic oxidative stress and inflammation.[30] Its activity increases in response to cellular damage caused by ROS and other pro-oxidative agents.[31] Elevated GGT levels reflect a state of increased GSH consumption, which is a critical antioxidant defense mechanism in the body.[32] GSH is depleted as it neutralizes ROS, leading to an upregulation of GGT activity to maintain cellular redox balance. In the MeS, GGT may indicate the presence of a pro-oxidative environment that accompanies IR and its associated metabolic derangements.[33] Elevated serum GGT levels are an independent marker of activation of systemic inflammatory responses and increased oxidative stress, which are of widespread importance in the development of atherosclerosis. Serum GGT concentrations are significantly associated with ascending aortic dilatation.[34] However, it has been reported to be associated with arterial stiffness, impaired aortic elasticity, and blood pressure.[35] This environment can exacerbate endothelial dysfunction, promote atherosclerosis, and ultimately increase the risk of CVD and all-cause mortality.[36] Many studies have shown that traditional cardiovascular risk factors, systemic inflammation, metabolic syndrome, increased oxidative stress, and several comorbidities are closely associated with high serum GGT levels.[37]

Early in the pandemic, it turned out that patients with cardiovascular comorbidities were most vulnerable to severe infection. The specificity of SARS-CoV-2 for the ACE-2 protein has raised concerns about cardiovascular system damage.[38,39] Similarly, in our study the effect of cardiovascular disease on mortality was statistically significant. However, contrary to the recommendations regarding the potential benefit of GGT measurements for cardiovascular disease risk assessment, in our study, GGT level did not have a different effect on disease severity and mortality in patients with COVID-19 infection and cardiovascular disease.

In a study by Kunutsor et al.[40] it was shown that GGT measurement was not associated with any clinically significant improvement in cardiovascular disease risk assessment. The close association between GGT and cardiovascular and metabolic risk factors clustered among patients with high GGT activity at least partially explains the association between GGT and death. However, the independent association of GGT with cardiac mortality has been interpreted as the enzyme's direct role in promoting atherosclerosis and related clinical events.[41] Although Ndrepepa et al.[42] found an independent relationship between GGT and cardiac mortality, they stated that GGT did not add information beyond the information provided by cardiovascular risk factors regarding the prediction of cardiac mortality. Similarly, in our study, although the serum GGT level was high in COVID-19, patients with severe disease, no difference was found in patients with cardiovascular disease, indicating that GGT does not provide increased risk information beyond those provided by concomitant cardiovascular risk factors.

Limitations

Our study has some limitations. This is a cross-sectional study and a potential causal relationship between COVID-19 and elevated serum GGT levels cannot be concluded. However, the findings of this study have some important implications for the determination of cardiovascular outcomes during the course of COVID-19 and for the management and prognosis of these patients

CONCLUSION

In the light of all this information, we planned this study because during a crisis such as the current COVID-19 pandemic, the serum GGT level and other cardiac prognostic markers that can identify cardiovascular risk help healthcare professionals to predict prognosis, thus identifying vulnerable patients at an earlier stage and providing them with an intensive treatment plan to prevent worsening outcomes. We think that cTnI may be a preferred option over CK-MB and BNP, mainly because of the worsening prognosis in COVID-19 patients and its high sensitivity in detecting myocardial damage. Although the independent association of GGT with cardiovascular disease suggests its usefulness in estimating risk, such information is insufficient to make judgments about its potential utility in classifying or predicting cardiovascular disease risk in individuals. However, although GGT provides no increasing benefit for predicting cardiovascular disease risk, its role in cardiovascular disease etiology and its potential causal relationship with cardiovascular disease deserves attention.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the. Kahramanmaraş Sütçü İmam University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 14.09.2021, Decision No: 07).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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